WO 2004/096212

Claims:

1. The use of a compound of formula (I) or a salt, N-oxide, hydrate or solvate thereof, in the preparation of a composition for inhibition of HSP90 activity:

wherein

 R_1 is a group of formula (IA):

$$-Ar^{1}$$
- $(Alk^{1})_{p}$ - $(Z)_{r}$ - $(Alk^{2})_{s}$ -Q (IA)

wherein in any compatible combination

Ar¹ is an optionally substituted aryl or heteroaryl radical,

Alk¹ and Alk² are optionally substituted divalent C₁-C₆ alkylene or C₂-C₆ alkenylene radicals,

p, r and s are independently 0 or 1,

 $\label{eq:Zis-O-,-S-,-(C=O)-,-(C=S)-,-SO2-,-C(=O)O-,-C(=O)NR^A-,-C(=S)NR^A-,-SO_2NR^A-,-NR^AC(=O)-,-NR^ASO_2- or -NR^A- wherein R^A is hydrogen or C_1-C_6 alkyl, and$

Q is hydrogen or an optionally substituted carbocyclic or heterocyclic radical;

- R₂ is (i) a group of formula (IA) as defined in relation to R₁;
 - (ii) a carboxamide radical; or
 - (iii) a non aromatic carbocyclic or heterocyclic ring wherein a ring carbon is optionally substituted, and/or a ring nitrogen is optionally substituted by a group of formula $-(Alk^1)_p-(Z)_r-(Alk^2)_s-Q$ wherein Q, Alk^1 , Alk^2 , Z, p, r and s are as defined above in relation to group (IA); and

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R₃ is hydrogen, or methyl, ethyl, n- or iso-propyl any of which being optionally substituted by hydroxy;

X is $-OR_4$ or $-NR_4R_5$ wherein R_4 and R_5 independently represent hydrogen or optionally substituted C_1 - C_6 alkyl, or R_4 and R_5 taken together with the nitrogen to which they are attached form an optionally substituted nitrogencontaining ring having 5-8 ring atoms.

2. The use as claimed in claim 1 wherein in the compound of formula (I), R_1 has formula (IB):

wherein R₆ is chloro, bromo, C₁-C₆ alkyl, or cyano.

3. The use as claimed in claim 1 wherein in the compound of formula (I) R_1 has formula (IC):

$$Q-(Alk^2)_s-(Z)_r-(Alk^1)_p$$

$$OH$$
(IC)

wherein Alk¹, Alk², p, r, s, Z and Q are as defined in claim 1 in relation to formula (IA), and R represents one or more optional substituents.

- 4. The use as claimed in claim 2 wherein R is –OH in the 4- position of the phenyl ring and the – $(Alk^1)_p$ - $(Z)_r$ - $(Alk^2)_s$ -Q substituent is in the 5- position of the phenyl ring.
- 5. The use as claimed in claim 4 wherein r is 0, and Q is hydrogen or optionally substituted phenyl.

6. The use as claimed in claim 5 wherein s is 0, p is 1 and Alk^1 is a non-substituted divalent C_1 - C_6 alkylene or C_2 - C_6 alkenylene radical.

- 7. The use as claimed in claim 5 wherein Alk^1 is $-CH_2$ -, $-CH_2CH_2$ -, $-CH_2CH_2$ -, or -CH=CH-.
- 8. The use as claimed in claim 4 wherein p, r and s are each 0
- 9. The use as claimed in any of the preceding claims wherein R_2 is phenyl, 2-, 3-, or 4-pyridyl, 2- or 3-furanyl, 2- or 3-thienyl, or thiazolyl, optionally substituted by one or more of methoxy, ethoxy, methylenedioxy, ethylenedioxy, fluoro, chloro, bromo, or trifluoromethyl.
- 10. The use as claimed in any of claims 1 to 8 wherein R_2 is optionally substituted phenyl.
- The use as claimed in any of claims 1 to 8 wherein R₂ is phenyl substituted in the 4 position by (i) C₁-C₆ alkoxy such as methoxy or ethoxy, fluoro, chloro, bromo, morpholinomethyl, piperazino, N-methylpiperazino, or piperidino, (ii)optionally substituted C₁-6 alkyl, eg optionally substituted methyl, ethyl, n-propyl or iso-propyl (iii) optionally substituted morpholino C₁-6 alkyl-, thiomorpholino C₁-6 alkyl-, piperazino C₁-6 alkyl-, methyl piperazino C₁-6 alkyl-, or diethylamino (iv) -NH₂, -NHR^A, -NR^AR^B, -NHCOR^A, -NHCOR^A, -NHCOR^A, -NHCOR^A, -NHSO₂OR^A, -NR^BSO₂OR^A, -NHCONH₂, -NR^ACONH₂, -NHCONHR^B, -NR^ACONHR^B, -NHCONR^AR^B or -NR^ACONR^AR^B wherein R^A and R^B are independently a (C₁-C₆)alkyl group or (v) optionally substituted piperadino, piperazino, morpholino or thiomorpholino.
- 12. The use as claimed in any of claims 1 to 8 wherein R_2 is a carboxamide radical of formula $-CONR^B(Alk)_nR^A$ wherein

Alk is an optionally substituted divalent alkylene, alkenylene or alkynylene radical,

n is 0 or 1,

R^B is hydrogen or a C₁-C₆ alkyl or C₂-C₆ alkenyl group,

R^A is hydroxy or an optionally substituted carbocyclic or heterocyclic ring,

or R^A and R^B taken together with the nitrogen to which they are attached form an N-heterocyclic ring which may optionally contain one or more additional hetero atoms selected from O, S and N, and which may optionally be substituted on one or more ring C or N atoms.

13. The use as claimed claim 12 wherein

Alk is an optionally substituted –CH₂-, –CH₂CH₂-, –CH₂-, –CH₂CH₂-, –CH₂-, –CH₂-,

n is 0 or 1,

R^B is hydrogen, methyl, ethyl, n- or iso-propyl, or allyl,

R^A is hydroxy, hydroxy and/or chloro-substituted phenyl, 3,4 methylenedioxyphenyl, pyridyl, furyl, thienyl, N-piperazinyl, or N-morpholinyl,

or R^A and R^B taken together with the nitrogen to which they are attached form a morpholino, piperidinyl, piperazinyl or N-phenylpiperazinyl ring.

- 14. The use as claimed in claim 12 wherein n is 0, R^B is hydrogen and R^A is hydroxy or an optionally substituted carbocyclic or heterocyclic ring.
- 15. The use as claimed in any of the preceding claims wherein R_3 is hydrogen.

16. The use as claimed in any of claims 1 to 14 wherein R_3 is other than hydrogen and the stereochemical configuration at the carbon centre to which it is attached is that of a D amino acid.

- 17. The use as claimed in any of the preceding claims wherein X is $-OR_4$ or $-NHR_4$ wherein R_4 is C_1 - C_6 alkyl, optionally substituted by hydroxy, or a primary- secondary, tertiary- or cyclic-amino group
- 18. The use as claimed in any of the preceding claims wherein X is $-NR_4R_5$ wherein R_4 and R_5 taken together with the nitrogen to which they are attached form a morpholino, piperidinyl or piperazinyl ring, the latter being optionally substituted by C_1 - C_6 alkyl on the second nitrogen.
- 19. A method of treatment of diseases or conditions mediated by excessive or inappropriate HSP90 activity in mammals which method comprises administering to the mammal an amount of a compound of formula (I) as defined in any of claims 1 to 15, or a salt, hydrate or solvate thereof, effective to inhibit said HSP90 activity.
- 20. The use as claimed in any of claims 1 to 18 or a method as claimed claim 16 for immunosupression or the treatment of cancer; viral disease, inflammatory diseases such as rheumatoid arthritis, asthma, multiple sclerosis, Type I diabetes, lupus, psoriasis and inflammatory bowel disease; cystic fibrosis angiogenesis-related disease such as diabetic retinopathy, haemangiomas, and endometriosis; or for protection of normal cells against chemotherapy-induced toxicity; or diseases where failure to undergo apoptosis is an underlying factor; or protection from hypoxia-ischemic injury due to elevation of Hsp70 in the heart and brain; scrapie/CJD, Huntingdon's and Alzheimer's disease.
- 21. A compound of formula (I) as defined in any of claims 1 to 18, or a salt hydrate or solvate thereof, for use in human or veterinary medicine.

22. A compound of formula (I) as defined in any of claims 1 to 18, or a salt, solvate or hydrate thereof.

- 23. A compound whose structure is set forth in any of the Examples herein, or a salt, solvate or hydrate thereof.
- 24. A pharmaceutical or veterinary composition comprising a compound as defined in claim 22 or claim 23, together with a pharmaceutically or veterinarily acceptable carrier.